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DATE: Wednesday, December 03, 2003

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<i>DB=USPT; PLUR=YES; OP=AND</i>			
L4	5545618.pn.	1	L4
L3	L2 same type II	67	L3
L2	L1 same diabetes	155	L2
L1	metformin same insulin	434	L1

END OF SEARCH HISTORY

0007247294 BIOSIS NO.: 199090031773

COMPARATIVE STUDY OF THE THERAPEUTIC EFFECTS OF GLIBENCLAMIDE OR THE FIXED COMBINATION OF GLIBENCLAMIDE PHENFORMIN WITH THOSE OF GLICLAZIDE OR CHLORPROPAMIDE

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JOURNAL: Acta Diabetologica Latina 27 (1): p11-22 1990

ISSN: 0001-5563

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: This study was designed to compare the therapeutic effects of glibenclamide or the fixed combination of glibenclamide-phenformin with those of gliclazide, chlorpropamide or biguanides in non-**insulin**-dependent **diabetes**. It is divided into two parts: (a) in the retrospective study (473 subjects), glucose control of patients who were transferred from chlorpropamide, gliclazide, glibenclamide, glibenclamide + biguanide or **metformin** to the fixed combination glibenclamide-phenformin in the same tablet (2.5 mg and 25 mg, respectively) was monitored. A statistically significant decrease of blood glucose and glycosylated hemoglobin values was found under the combination of glibenclamide-phenformin contained in the same tablet in contrast to the values obtained with the treatment with glibenclamide, gliclazide, chlorpropamide, combination of glibenclamide and biguanides, **metformin**, and **insulin**. (b) In the prospective study (57 subjects), the patients were transferred from chlorpropamide or gliclazide to glibenclamide for 3 months and then reallocated to the previous treatment for 3 additional months. It was found that under glibenclamide, glucose control was significantly better than under chlorpropamide or gliclazide. In conclusion, glibenclamide, a second generation sulfonylurea, and the fixed combination glibenclamide-phenformin in the same tablet are more effective compared to the other antidiabetic agents here studied and lead to a better

/9/1 (Item 1 from file: 149)
DIALOG(R) File 149:TGG Health&Wellness DB(SM)
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01292140 SUPPLIER NUMBER: 09860819 (THIS IS THE FULL TEXT)

Diabetes research update. (Cover Story)

Beaser, Richard S.; Weir, Gordon C.; Hill, Joan

Diabetes in the News, v10, n1, p6(7)

Jan-Feb,

1991

DOCUMENT TYPE: Cover Story PUBLICATION FORMAT: Magazine/Journal ISSN:

0893-5939 LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE:

Consumer

WORD COUNT: 2536 LINE COUNT: 00212

TEXT:

Section I Preventing Type I Diabetes

Scientists are coming close to discovering why and how Type 1, insulin-independent diabetes occurs.

They are developing tests which help to identify persons at risk for this type of diabetes, and which also can identify the person who is developing type I diabetes-years before symptoms show up and before the cells of the pancreas that produce insulin are completely destroyed.

And they are experimenting with methods to prevent Type I diabetes or to stop the progression of diagnosed Type I diabetes.

Some of these tests are available in medical centers at the present time.

The treatments (prevention of or halting the disease) are still experimental and may not be widely available for many years. But scientists are working on a number of ways to slow or stop development of Type I diabetes.

Scientists are studying the protective effects that come from administering insulin to people who have tested "positive" for the early stages of developing diabetes (pre-diabetes) but who have not developed full-blown Type I diabetes.

Other scientists have been using, on an experimental basis, anti-rejection drugs such as cyclosporine, prednisone and azathioprine, to prevent the destruction of insulin-producing beta cells in newly diagnosed diabetics.

They are also studying the effectiveness of using anti-rejection drugs to slow or stop the destruction of insulin-producing cells in persons who are well down the road toward developing Type I diabetes.

Research studies do show some degree of effectiveness of this approach, but the presently available anti-rejection drugs have many serious side effects (such as kidney damage) which limit their widespread use.

Also, the beneficial effects of these drugs last only while the patient continues to take the medication.

One day, scientists may be able to insert a healthy gene to substitute for the diabetes gene" and thus prevent diabetes.

Many other scientists are continuing the search for safe but effective drugs that will stop the destruction of the cells that produce insulin. Preventing Type II Diabetes

Scientists know much less about why and how Type II, noninsulin-dependent diabetes, occurs than they know about Type I diabetes.

They do know that Type II diabetes seems to run in families, and that people who are overweight and over the age of 40 are most likely to develop this kind of diabetes.

People with this form of diabetes produce some amount of insulin (some even have higher than normal amounts of insulin in their bloodstreams).

But people with Type II diabetes seem to resist insulin's effort to

unlock body cells so that glucose can enter the cells and be used for energy.

In addition, many people with Type II don't produce enough insulin to meet their bodies' needs (because of insulin resistance and, perhaps, other factors). For some reason, their bodies' needs for insulin seem to be higher than those for people without diabetes.

Many people with Type II don't have enough cells producing insulin in their pancreas, and seem to lose more and more of these cells over the years.

Before any preventive measures for Type II diabetes can be developed, scientists need to know more about what causes insulin resistance and the inadequate production of insulin. They are also searching for genes which may cause this disease.

Section 2 Treating Type I Diabetes 1 Transplants,

Much of the effort of many research scientists has been in the area of transplants-to replace the defective" body part that breaks down in Type I diabetes.

That body part is the pancreas gland itself, or the cells within the pancreas that produce insulin.

Trying to replace a broken or defective part is a common approach in many fields, including medicine.

Since the first attempted pancreas transplant in the mid1960s, this approach has produced much hope in the field of diabetes research.

There have been major advances and successes in transplantation, too.

But the problem is that once an organ, or part of an organ, has been transplanted from a donor to a recipient (in this case, a person with diabetes), the recipient's body attempts to destroy the transplant (which it considers to be a foreign invader). This is called rejection.

Rejection, which is a problem in all types of transplants, is much more severe when doctors try to transplant a pancreas, or part of a pancreas, into someone with Type I diabetes.

The reason for this is that Type I diabetics have developed this disease because their bodies have destroyed their own insulin-producing cells.

Transplantation of new cells into this destructive environment becomes quite risky.

To overcome this dual-destructive process found in people with diabetes, anti-rejection drugs must be administered to the recipient of the transplant.

As stated in Section I, the presently available anti-rejection drugs can produce severe side effects, and can cause health problems as undesirable as diabetes itself.

There have been several approaches to transplantation used to provide healthy insulinproducing cells to the person with Type I diabetes. Two approaches use whole pancreases (obtained from cadavers) or segments of pancreases (which can be donated by a living person). A third, highly experimental approach has been to transplant insulin-producing cells (obtained primarily from cadavers).

Finding adequate numbers of donors presents a challenge, not only in diabetes but also in other organ transplant areas (such as kidney, heart and liver transplants). There are many more potential recipients waiting for transplants than there are donors.

There is serious concern about placing the donor of a pancreas segment at risk for future development of diabetes. Scientists are studying this problem at the present time.

One area that shows great promise is the transplantation of insulin-producing islet cells. Scientists are working on methods to pretreat cells with ultraviolet rays before they are transplanted, to protect them against rejection.

Other scientists are working on placing these cells inside plastic bubbles or membranes to protect them. At the present time, most medical centers doing transplants will do these procedures on persons with diabetes

who also are having kidney transplants because of kidney failure related to diabetes). Since the recipients of kidney transplants must have anti-rejection treatment anyway, they are not at increased risk when they take these potentially toxic drugs after implantation of a whole or partial pancreas or islet cells.

2 Artificial Pancreas

If your pancreas is not functioning properly, one of the ways to handle this problem is to replace it. Transplanting healthy, functioning organs (whole, partial or cells only) is one approach. The other approach is to create an artificial (man-made) pancreas.

The closest thing to an artificial pancreas that scientists have developed is an "open loop" insulin infusion pump. This device is called "open loop" because the person using it must instruct the pump to release a specific amount of insulin. The user must measure his or her own blood glucose levels and instruct the pump to deliver the appropriate amounts of insulin based on these measurements.

Most "open loop" pumps are worn externally, with tubes from the unit leading to a needle that is inserted under the skin to deliver the insulin. Recently, some types of insulin pumps have been implanted (in the body of the user), and these pumps deliver insulin directly into the circulatory system. The implanted pump's reservoir holds several weeks' worth of insulin, which can be replenished by injection into the pump when needed.

But the implanted pump of today still requires the user to frequently measure blood glucose levels and then instruct the pump (by electronic signals) how much insulin should be delivered.

The goal in pump research is to produce an implantable closed loop" pump system, which measures blood glucose levels automatically and then releases insulin based on these measurements. Such a system would imitate the healthy body's response to glucose.

Unfortunately, the development of an automatic glucose measuring system has proven to be a difficult task for scientists.

The only closed loop system now available is a relatively large instrument that sits on a cart and is used only in research studies at medical centers.

Miniaturizing a glucose sensor so that it can be implanted is possible. Making a sensor that works at 100% accuracy and efficiency once it is implanted is another story.

The implantable "closed loop" system, therefore, is some years away from perfection.

3 Insulin Delivery

Almost every year some scientists report on new to deliver insulin (other than by injection).

In recent years there have been glowing reports about the development of an insulin nasal spray, an oral dosage form of insulin and even an insulin patch. Studies are now going on to determine the effectiveness of an insulin nasal spray and an insulin patch.

Researchers are still working on methods to protect insulin from being destroyed by digestive juices in the stomach, by encapsulating insulin in plastic or fat bubbles.

The studies of insulin nasal spray, on humans, have shown that this method of administration poses some significant problems, since the absorption of insulin from nasal tissue seems to vary from dose to dose. If this delivery method ever becomes practical, it probably will be used to supplement insulin injections, not replace them.

Studies on the insulin patch are still in their early stages, and it is impossible at this time to predict their outcomes.

Other scientists are working on developing genetically designed forms of insulin that are stronger and more predictable in absorption than present forms. Treating Type II Diabetes 1 Oral Medication The "second generation" oral agents have been on the market in the United States for only a few years, and are now being widely and successfully used by Type II diabetics who cannot control their disease by diet and exercise alone. Both the first and second generation drugs are in the family of chemicals called sulfonylureas.

Another type of oral agent, from the biguanide family, one day may be added to the arsenal of drugs available to control blood glucose.

One of the biguanides was marketed in this country years ago, but was withdrawn because of side effects it caused. Newer, safer biguanides have been developed and are available in many countries throughout the world.

United States clinical testing with a biguanide called metformin is now underway, but approval for marketing may be years away. This agent is believed to work differently from the other oral agents.

Sulfonylureas stimulate insulin production and may partially correct insulin resistance. Metformin is believed to work by slowing glucose production in the liver, or by reducing glucose absorption in the intestine. In effect, the drug slows the rise of blood glucose levels.

Scientists believe that this drug, when and if it is approved, will be valuable for diabetics who have been unable to control their blood glucose levels with either the first or second generation sulfonylurea oral agents. Other Research News

Nutrition 1 Fat Substitutes

Early last year the Food and Drug Administration approved the marketing of the first reduced calorie fat substitute.

This product, which is called Simplese, is made of proteins from egg whites and milk, and sugar. Because it is destroyed by heat, this fat substitute cannot be used in cooking, and is restricted to use in such products as frozen desserts, mayonnaise, cheeses, yogurt, dips and spreads. Since it contains sugar and calories, it must be counted in a diabetes meal plan (either Exchange or Calorie-Counting).

Another fat substitute is undergoing review by the FDA for approval to be marketed. This substitute may be made available later this year. 2 Carbohydrate Blockers

Scientists, for many years, have been working on the development of products called "carbohydrate blockers" or "starch blockers."

In theory these "blockers" should allow you to eat more foods that are high in carbohydrates, and, at the same time lose weight and keep your blood glucose levels under control.

Unfortunately theory and practice don't always coincide. Research studies have not shown that these agents can effectively and safely do what they are intended to do.

It may be some time, if ever, before a safe and effective agent is developed that will block the digestion of carbohydrates. Complications

By the end of 1993 (or early 1994) the results of the Diabetes Control and Complications Trial may be released.

You (and other diabetics and health professionals) will then learn whether intensive therapy (three or four injections of insulin a day, or use of an insulin infusion pump, plus frequent blood glucose monitoring) will prevent complications better than standard therapy (two insulin injections a day).

While few health professionals would disagree that good diabetes control is needed to reduce the risks for complications, it has been difficult to determine what is good enough control.

Hopefully, the final report from this study will provide the answers to this problem.

In addition to this trial, other scientists are studying the relationships of various factors, including diabetes control, complications and heredity.

Scientists are looking for answers to the question of how high blood glucose levels actually contribute to the development of complications. Other scientists are studying whether heredity plays a role in determining if an individual will develop complications.

One popular theory is that excess glucose is converted into a substance called sorbitol in the body, and that excess sorbitol leads to complications such as neuropathy and retinopathy.

Basing their work on this theory, scientists are working to develop drugs that block the production of destructive sorbitol.

The class of drugs most promising in this function is called aldose reductase inhibitors.

Early studies with these drugs found that they did produce some beneficial results, particularly in diabetics with neuropathy and retinopathy.

Unfortunately, the drugs that produced these beneficial effects also produced harmful side effects.

Testing is now underway on modifications of these drugs that will produce fewer side effects while still benefiting people with neuropathy and retinopathy.

While research is continuing on ways to treat retinopathy with medication, significant progress has been made in the treatment of retinopathy with laser beams.

Two different types of laser treatment have shown great promise. One is the focal laser treatment, in which the laser beam is used to seal the leaky retinal blood vessels that cause swelling of the eye (edema).

The other is the scatter laser treatment, in which the laser beam is used to produce many tiny burns scattered throughout the retina (without burning the macula), and results in the slowing of new blood vessel growth, and reduced bleeding and scar tissue development.

Another diabetes complication, nephropathy (kidney disease), has been targeted by many scientists.

Studies have shown that early detection of kidney function problems (through simple dip-and-read urine tests that detect microscopic amounts of protein), control of high blood pressure, diet and medication treatment will slow the destruction of kidney function.

A low protein diet is also being studied to see if it can slow the progression of kidney disease.

Hereditry is believed to play a role in determining whether a person is at risk for kidney and other problems, so genetic research is underway to identify individuals who are at increased risk for complications.

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SPECIAL FEATURES: illustration; photograph

DESCRIPTORS: Pancreas--Research; Diabetics--Food and nutrition; Pancreas--

Transplantation; Diabetes, Non-insulin-dependent--Research; Diabetes--

Complications; Diabetes--Research

FILE SEGMENT: HI File 149

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05512361 Genuine Article#: RV842 Number of References: 8
Title: **INSULIN** ALONE OR **INSULIN** + ORAL-AGENTS IN THE TREATMENT
 OF **TYPE-II** DIABETIC-PATIENTS AFTER ORAL-AGENTS FAILURE
Author(s): CARTA Q; TROVATI M; DANI F; CASELLE MT; VITALI S; CAVALOT F;
 MULARONI E; ROCCA G
Corporate Source: SAN GIOVANNI BATTISTA HOSP,DIABET CLIN/TURIN//ITALY/;
 UNIV TURIN,INST INTERNAL MED,CATTEDRA CLIN MED GEN & TERAPIA MED
 3/I-10126 TURIN//ITALY/; SAN GIOVANNI BATTISTA HOSP,STAT
 UNIT/TURIN//ITALY/
Journal: IRCS MEDICAL SCIENCE-BIOCHEMISTRY, 1983, V11, N12, P
 1113-1114
Language: ENGLISH Document Type: ARTICLE

0005918711 BIOSIS NO.: 198835015816

COMPARATIVE STUDY BETWEEN SULFONYLUREA-**INSULIN** COMBINATION THERAPY
WITH SPECIAL REFERENCE TO A GROUP OF PATIENTS WITH RENAL FAILURE AND
METFORMIN-INSULIN COMBINATION THERAPY IN **TYPE II**
DIABETES

BOOK TITLE: BACHMANN, W., N. LOTZ AND H. MEHNERT (ED.). **INSULIN**
/SULFONYLHARNSTOFF: KOMBINATIONSTHERAPIE BEI TYP-II-**DIABETES** (
INSULIN/SULFONYLUREA: COMBINATION THERAPY IN TYPE II
DIABETES); 2ND SYMPOSIUM, MUNICH, WEST GERMANY, OCTOBER 28, 1986.
VIII+167P. S. KARGER AG: BASEL, SWITZERLAND; NEW YORK, NEW YORK, USA.
ILLUS

AUTHOR: KNICK B (Reprint); ROECKEL A; PANITZ N; GROTH U

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p98-106 1988

ISBN: 3-8055-4601-7

DOCUMENT TYPE: Book; Meeting

RECORD TYPE: Citation

LANGUAGE: GERMAN

04363706 84005344 PMID: 6352352

Biguanides. A review of history, pharmacodynamics and therapy.

Schafer G

Diabete & metabolisme (FRANCE) May-Jun 1983, 9 (2) p148-63,

ISSN 0338-1684 Journal Code: 7604157

Document type: Journal Article; Review

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

This review on biguanides gives a general survey of biguanide actions on many metabolic models in vivo and in vitro. It focuses especially on the comparison of the 3 antidiabetic biguanides, of which **metformin** is discussed as the only oral antidiabetic biguanide useful in treatment of **type-II diabetes** with a minimum risk of side effects when applied in a well controlled regime. Pharmacokinetics, pharmacodynamics, hypotheses on the molecular mode of action, and implications for therapy are discussed. (190 Refs.)

Record Date Created: 19831123

Record Date Completed: 19831123

5241771 EMBASE No: 1993009856

Assessment of metabolic profile and body mass index (BMI) in **type**
II diabetics treated with **metformin** and **insulin**

Masud F.; Hasan M.; Abaidullah S.; Intekhab

Department of Medicine, Lahore Pakistan

Specialist (SPECIALIST) (Pakistan) 1992, 9/1 (29-34)

CODEN: SPCAE ISSN: 1017-4699

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

03222735 EMBASE No: 1986110312

Secondary failure of oral hypoglycemic agents in **type II diabetes** mellitus. Effect of blood glucose control by means of intravenous **insulin** infusion

ECHEC SECONDAIRE DES ANTIDIABETIQUES ORAUX. INTERET DES INFUSIONS INSULINIQUES INTRAVEINEUSES

Augustin-Pascal I.; Richard J.L.; Rodier M.; et al.

Clinique des Maladies Metaboliques et Endocriniennes, Hopital Lapeyronie, F 34059 Montpellier Cedex France

Diabete et Metabolisme (DIABETE METABOL.) (France) 1986, 12/1 (1-5)

CODEN: DIMED

DOCUMENT TYPE: Journal

LANGUAGE: FRENCH SUMMARY LANGUAGE: ENGLISH

A temporary strict blood glucose control was achieved by means of intravenous **insulin** infusion in 37 non **insulin**-dependent diabetic patients with secondary drug failure to reinduce the efficacy of oral hypoglycemic agents. This procedure was successful in 18 patients (48.6%) resulting in better glycemic response to oral hypoglycemic agents. Results remained identical 6 and 12 months later. This improvement does not seem related to an increase in **insulin** secretion as urinary C-peptide and basal and glucagon-stimulated plasma C-peptide were identical before and after **insulin** infusion. We suggest that a decrease in **insulin** resistance, not tested in this study, may explain the beneficial effect of normoglycemia in our patients.

itle: ORAL ANTIDIABETIC DRUGS FOR THERAPY OF **TYPE-II**

DIABETES - PRO AND CONTRA

Author(s): MEHNERT H

Corporate Source: STADT KRANKENHAUS, AKAD LEHRKRANKENHAUS, MED ABT 3, KOLNER
PL 1/D-8000 MUNICH 40//FED. REP GER/

Journal: MEDIZINISCHE WELT, 1991, V42, N11, P919-922

Language: GERMAN Document Type: ARTICLE

Abstract: Far too many of the more than 3 million **type II**

diabetics in Germany are treated with oral antidiabetic drugs, which are started too early and withdrawn too late. Nevertheless, for the correct indications the available medicaments - acarbose, **metformin** and the sulphonylureas - are certainly valuable additions to treatment. New findings on the metabolic syndrome have provided cause for changing our way of thinking: substances with non-insulinotropic actions should be the treatment of choice, even in cases where sulphonylureas must be prescribed, if necessary to supplement acarbose or **metformin**. Owing to the weaker blood sugar lowering effects of the former drugs this is not seldom the case. In case of secondary failure of oral therapy a combination of **insulin** with glibenclamide should be prescribed in preference to **insulin** monotherapy.

0008211458 BIOSIS NO.: 199293054349

NON-**INSULIN**-DEPENDENT **TYPE II DIABETES MELLITUS**

AUTHOR: RODGER W (Reprint)

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JOURNAL: Canadian Medical Association Journal 145 (12): p1571-1581

1991

ISSN: 0820-3946

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: Non-**insulin**-dependent (**type II**) **diabetes**

mellitus is an inherited metabolic disorder characterized by hyperglycemia with resistance to ketosis. The onset is usually after age 40 years. Patients are variably symptomatic and frequently obese, hyperlipidemic and hypertensive. Clinical, pathological and biochemical evidence suggests that the disease is caused by a combined defect of **insulin** secretion and **insulin** resistance. Goals in the treatment of hyperglycemia, dyslipidemia and hypertension should be appropriate to the patient's age, the status of diabetic complications and the safety of the regimen. Nonpharmacologic management includes meal planning to achieve a suitable weight, such that carbohydrates supply 50% to 60% of the daily energy intake, with limitation of saturated fats, cholesterol and salt when indicated, and physical activity appropriate to the patient's age and cardiovascular status. Follow-up should include regular visits with the physician, access to **diabetes** education, self-monitoring of the blood or urine glucose level and laboratory-based measurements of the plasma levels of glucose and glycated hemoglobin. If unacceptably high plasma glucose levels (e.g., 8 mmol/L or more before meals) persist the use of orally given hypoglycemic agents (a sulfonylurea agent or **metformin** or both) is indicated. Temporary **insulin** therapy may be needed during intercurrent illness, surgery or pregnancy. Long-term **insulin** therapy is recommended in patients with continuing symptoms or hyperglycemia despite treatment with d

01292140 SUPPLIER NUMBER: 09860819 (THIS IS THE FULL TEXT)

Diabetes research update. (Cover Story)

Beaser, Richard S.; Weir, Gordon C.; Hill, Joan

Diabetes in the News, v10, n1, p6(7)

Jan-Feb,

1991

TEXT:

Section I